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AN INTERSPECIES COMPARISON OF THE TISSUE DISTRIBUTION OF WR-2721, A RADIOPROTECTIVE DRUG

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Pre-irradiation intravenous administration of the radioprotective drug S-2-[3-aminopropylamino]ethylphosphorothioic acid (WR-2721) has potential value in radiotherapy because it doubles the radiation resistance of normal mouse tissues while affording only minimal protection to tumors (1). Deficient deposition of WR-2721 in tumor tissue has recently been demonstrated (2,3), and this is thought to be a major reason for the preferential protection of normal tissues by the drug.

Data originally obtained in our study using the mouse and rat (2) indicated that the tissue distribution of WR-2721 was possibly more closely related to dose per unit surface area than to dose per unit weight. To test this hypothesis an interspecies comparison of the tissue distribution of ^{35}S-labeled WR-2721 was carried out in normal mice, rats, rabbits, and dogs at 15 and 30 minutes after intravenous administration.

The animals used were male C57BL/6 mice, male Buffalo rats, female New Zealand white rabbits, and both sexes of laboratory grade beagle dogs. (Results were pooled since no sex difference was evident.) Both unlabeled and ^{35}S-labeled WR-2721 (9.4 μCi/mg) were synthesized according to the method of Piper et al. (4) and were assessed to be of greater than 99% purity (5). The appropriate mixture of labeled and unlabeled WR-2721 was dissolved in distilled water immediately before use. Mice, rats, and rabbits received 10 μCi ^{35}S/kg and dogs received 20 μCi ^{35}S/kg. Mice and rats were killed by exsanguination following light ether anesthesia, while rabbits and dogs were given an intravenous overdose of sodium pentobarbital. Tissue processing, solubilization, and counting have been described elsewhere (2).

The WR-2721 dose administered to each species was that which would produce the same tissue concentrations in all species, if drug dose per unit surface area were the sole factor in determining tissue concentrations. Since the respective surface area correction factors are 1.0 for the mouse, 1.43 for the rat, 2.74 for the rabbit, and 4.82 for the dog (6), the administered doses, in terms of dose per unit body weight, were 100 mg/kg for the mouse, 70.0 mg/kg for the rat, 36.5 mg/kg for the rabbit, and 20.8 mg/kg for the dog.

For purposes of analysis, we normalized the averaged WR-2721 tissue concentrations (μg/g) for each species. A normalization factor for each mouse tissue was derived which converted the concentration for each mouse tissue to 100 μg/g; each "mouse tissue normalization factor" was then multiplied by the observed concentration of the same tissue in the other species. A log-log plot of these normalized values for each tissue as a function of animal weight is given in Fig. 1 for the 15 minute data. Data obtained at 30 minutes was similar. Theoretical lines describing perfect "dose per unit surface area" and "dose per unit body weight" relationships are included.

The data in Fig. 1 suggests that the surface area and body weight exert equal effects on the tissue concentration of WR-2721. The results further suggest that lower absolute doses of WR-2721 in the human, possibly as low as 20 mg/kg, may provide a radioprotective effect equivalent to that produced from 100 mg/kg in the mouse, i.e., a 50-80% increase in radiation resistance.

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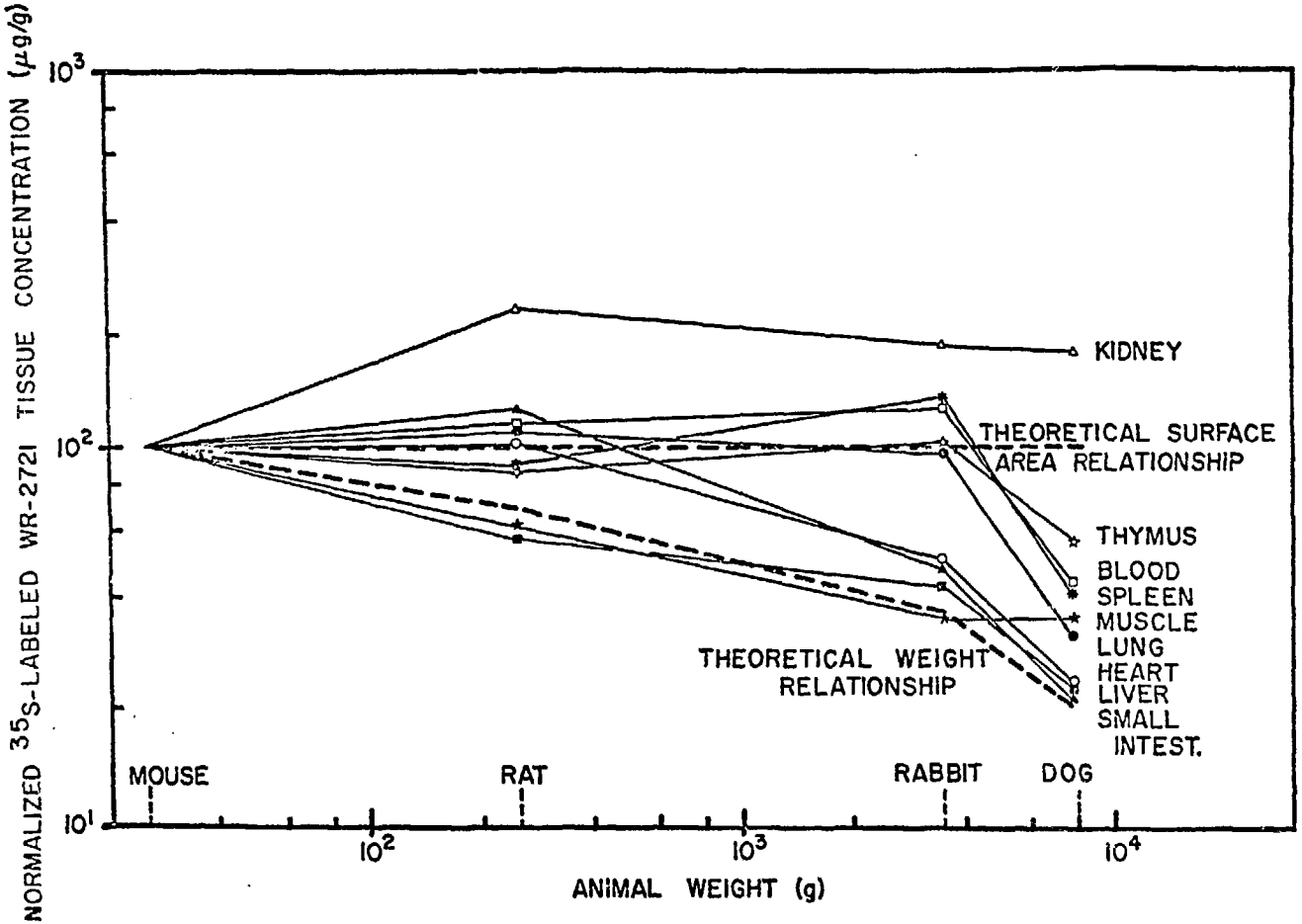
Legend

Fig. 1 Relationship of normalized tissue concentrations of ^{35}S-labeled WR-2721 to body weights in various tissues of the mouse, rat, rabbit, and dog at 15 minutes postinjection.


NORMALIZED ^{35}S-LABELED WR-2721 TISSUE CONCENTRATION (μg/g)
10^3
10^2
10^1
KIDNEY
THEORETICAL SURFACE AREA RELATIONSHIP
THYMUS
BLOOD
SPLEEN
MUSCLE
LUNG
HEART
LIVER
SMALL INTEST.
THEORETICAL WEIGHT RELATIONSHIP
MOUSE
RAT
RABBIT
DOG
10^2
10^3
10^4
ANIMAL WEIGHT (g)